Synthesis of polisubstituted aromatic compounds

Theses of PhD dissertation

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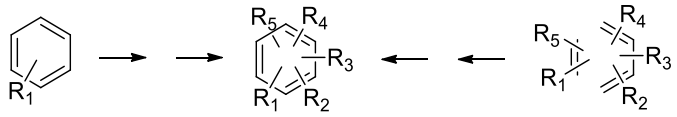
1 Introduction

Many polisubstituted benzene derivatives and heterocycles can be found in numerous natural products. Due to their divers properties they are applied in several applications in different areas such as pharmaceutical, cosmetics, plastics or electronics industry. Therefore the simple, selective synthesis of these compounds is highly desirable from inexpensive materials using economical and scalable methods. In the last hundred years several efficient strategies were developed and used for manufacturing aromatic and heterocyclic compounds, but in many cases, simple and scalable syntheses of important classes of compounds still do not exist.

Conventionally polisubstituted benzene derivatives are made through consecutive aromatic electrophilic and nucleophilic substitutions. With this method the syntheses became more and more complicated with increasing number of the substituents due to their different directing, activating or inhibitory effect. Another option is the [2+2+2], [4+2] or [3+3] annulation of the benzene ring, which enables to shorten the synthesis, but to ensure the appropriate regioselectivity is challenging (***Scheme 1***).



Scheme 1. *Synthesis of benzene derivatives with aromatic substitutions or annulation*

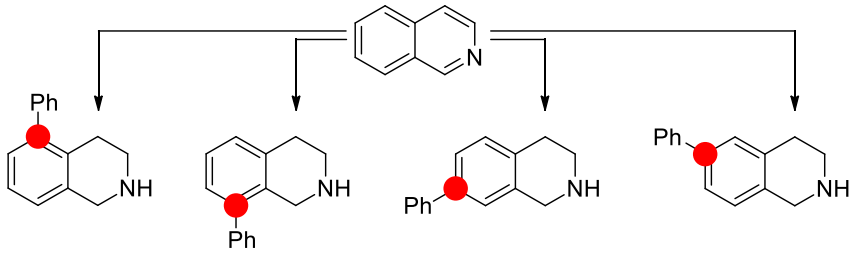
During my PhD work I did research on the synthetic problem of the synthesis of polisubstituted aromatic compounds and to develop a scalable synthesis for two classes of compounds:

First the selective substitution of the isoquinolines was investigated, which are important from pharmaceutical point of view. Secondly the de novo synthesis of benzene derivatives with multiple substituents was investigated, and they were used to make a new type of phase transfer catalysts with biphenyl backbone.

2 Aims

For the construction of the isoquinoline framework several methods exist, but all of them have their limits. The classic methods (the Bischler-Napieralszky, the Pictet-Gams, the Pictet-Spengler and the Pomeranz-Fritsch reaction) work well with electron donating compounds applying harsh and acidic conditions, therefore the function group tolerance is low. Promising alternatives are the recently developed transition metal catalyzed synthesis, but the accessibility of the starting materials may set limit for their application.

In my doctoral research we set ourselves the goal to develop a divergent strategy, which enables the selective substitution of the carbocycle of the isoquinoline. To demonstrate the utility of the methodology the attachment of a phenyl group was aimed at any of the four possible vacant positions of its carbocyclic core (***Scheme 2***).

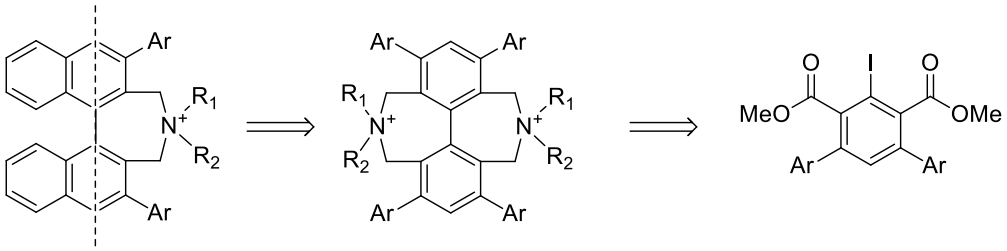


Scheme 2. *Concept of the divergent synthesis*

Furthermore we aimed to synthetize the necessary isoquinoline intermediates in a simple, scalable way and to apply these intermediates in natural products synthesis.

The asymmetric phase transfer catalysis (PTC) is hardly utilized in industrial processes despite of its several advantages and wide applicability. One of the reasons is that the availability of the efficient catalysts are limited, therefore their price are high. Although the catalyst load can be reduced under 1 %, the molecule weight of the catalysts still high (e.g. the simplified Maruoka catalyst containing 3,4,5-trifluoromethyl groups has 669 g/mol/reaction center)

Therefore we set ourselves the goal to synthesize a new, chiral PTC catalyst comprising a biphenyl core with C_2 symmetry based on the successfully applied Maruoka catalyst. This new type of catalyst would contain the active site of the model catalyst twice (***Scheme 3***).



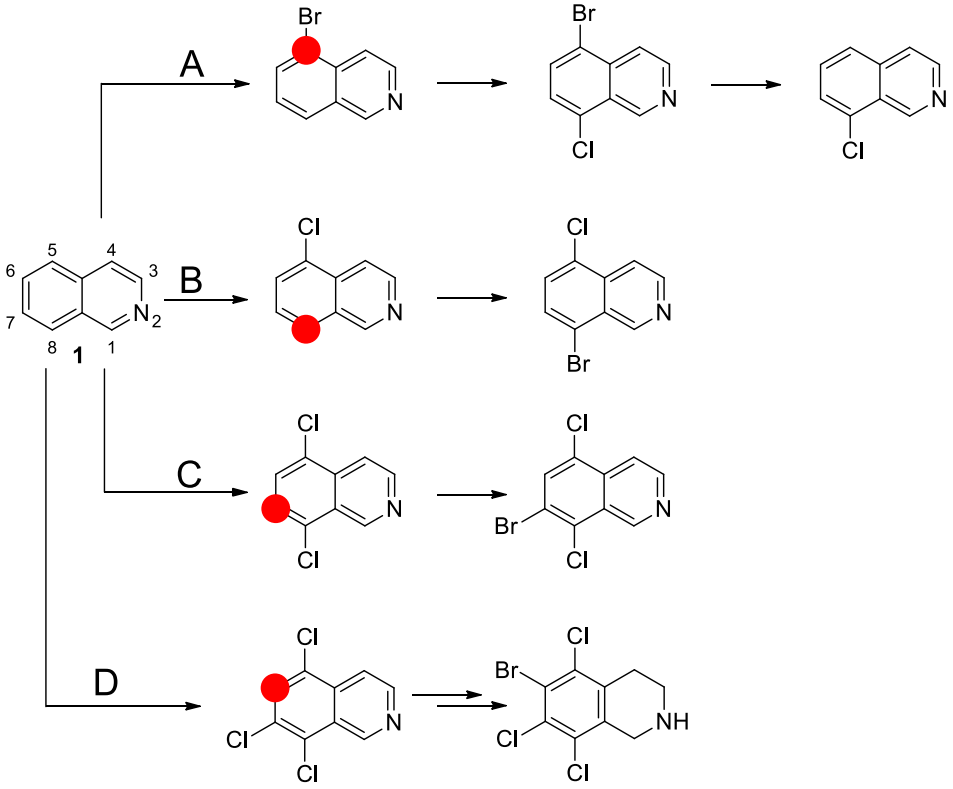
Scheme 3. *Design of new, biphenyl based chiral PTC catalyst and the key intermediate of its synthesis*

In the synthesis of the designed catalyst the key intermediates are the pentasubstituted iodobenzene derivatives with the appropriate aromatic groups. The construction of these halogenated compounds is a synthetic challenge in itself, therefore we also aimed to realize a simple, rapid and scalable synthesis of these building blocks.

3 Results

The main results and conclusions can be summarized as follows:

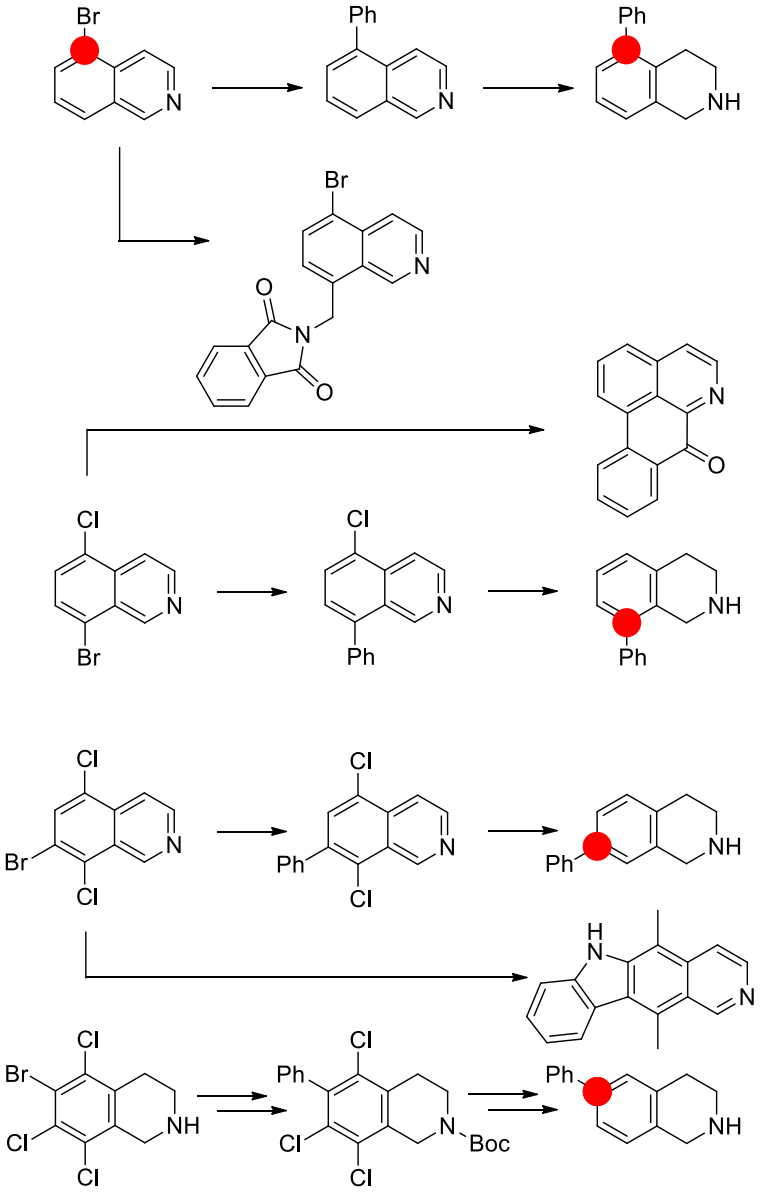
1. A divergent strategy was developed for the selective substitution of isoquinolines to access the four possible vacant positions of the carbocycle core. This was realized through applying the principle of regioexhaustive functionalization through consecutive aromatic electrophilic substitution using chlorine as an easily removable „site-silencing" group and bromine for activation, which gives the opportunity to reach less reactive positions (***Scheme 4***).



Scheme 4. *Application of the regioexhaustive method for the isoquinoline*

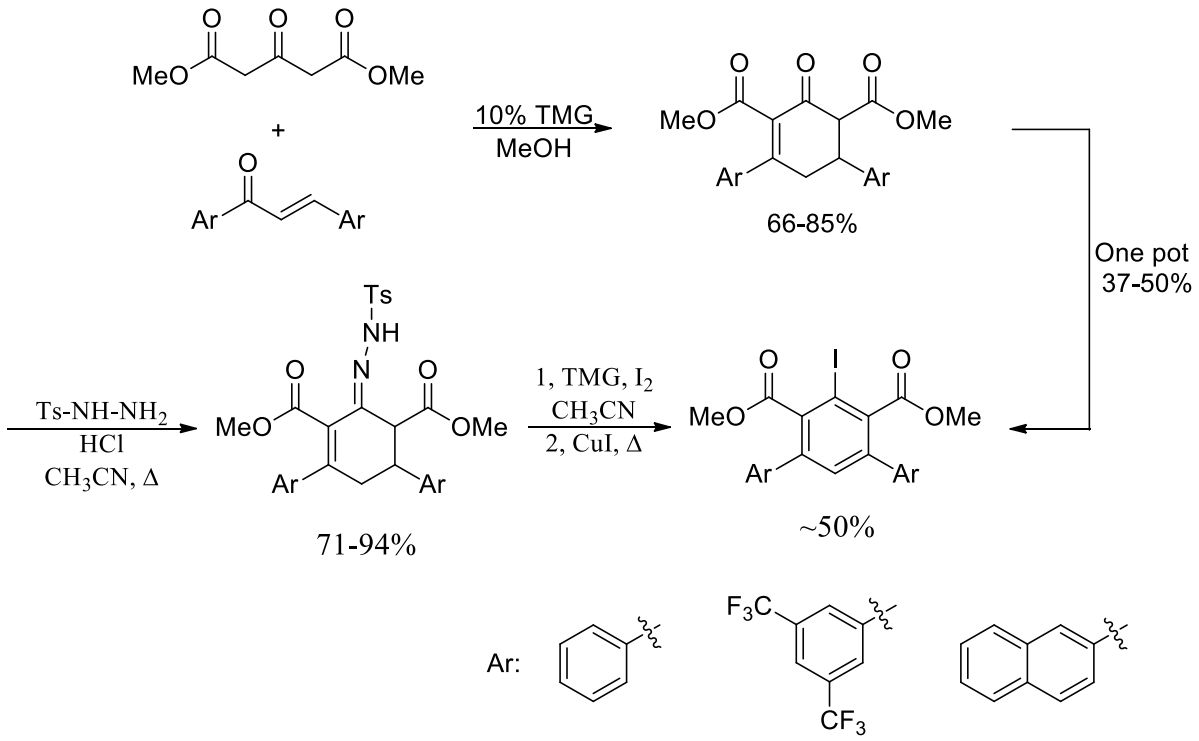
2. Different halogenated isoquinolines were prepared in a scalable manner using the developed regioexhaustive methodology. These derivatives are suitable for further functionalization (***Scheme 4***).

3. The simple functionalization of the synthesized halogenated aromatic compounds was demonstrated by their transformation into otherwise hardly accessible compounds through Suzuki-coupling and subsequent hydrogenation. The synthetic value of these chloro-bromo isoquinolines was proved by realization of short, concise synthesis to the core of the oxoaporphine and to the ellipticine (***Scheme 5***).



Scheme 5. *Transformation of the halogenated isoquinoline derivatives*

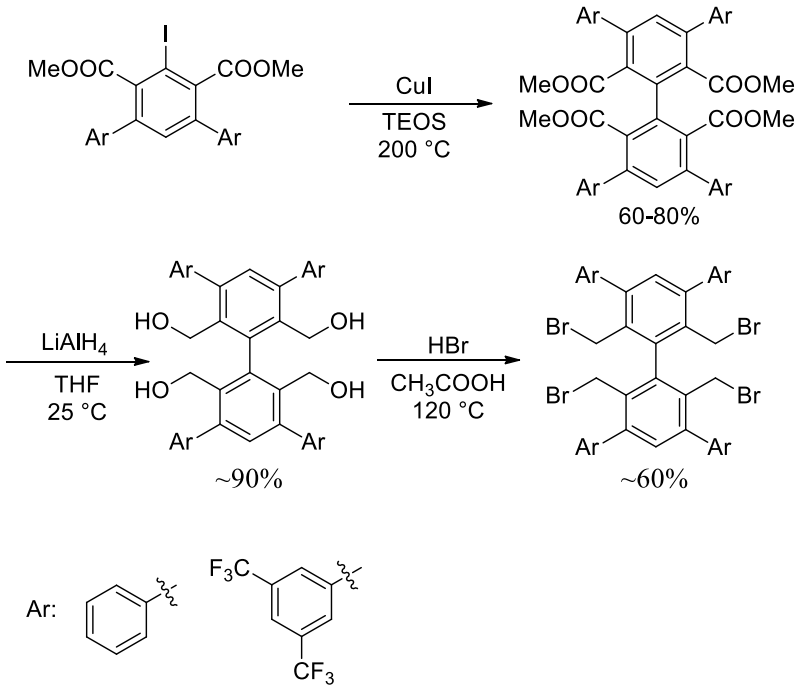
4. In the second part of my work, new chiral biphenyl PTC catalysts were prepared in a scalable manner, in which the active center of the successful Maruoka catalyst was doubled. In the course of the synthesis of the chiral PTC catalyst, 2,3,4,5-tetrasubstituated iodobenzene derivatives were constructed using *de novo* [3 + 3] annulation, in which suitable tosylhydrazone intermediates were transformed into polisubstituated iodobenzenes using a new methodology (***Scheme 6***).



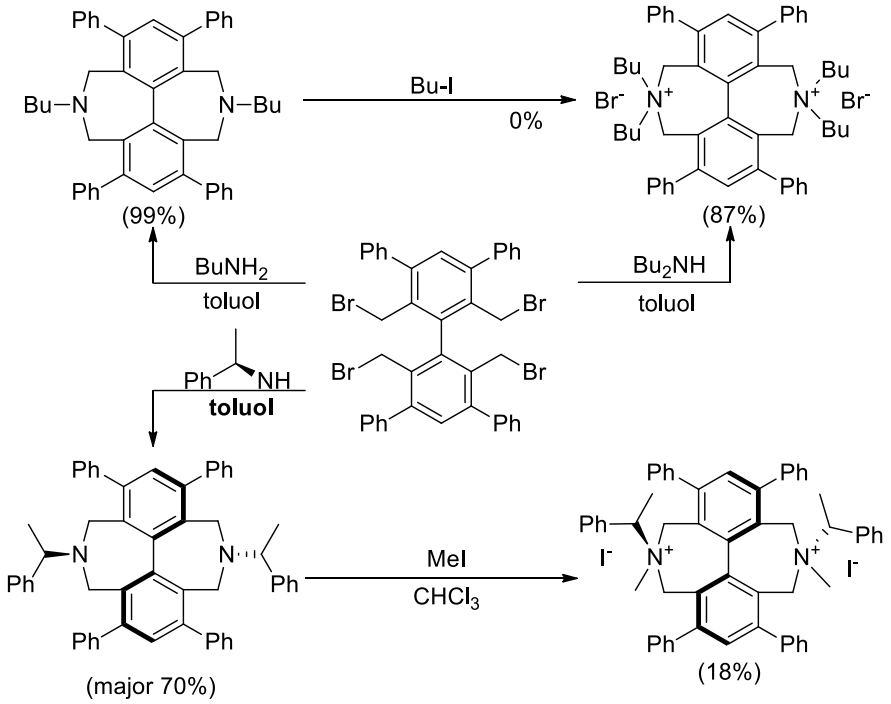
Scheme 6. *Synthesis of tetrasubstituted iodobenez derivatives*

The synthesis is based on easily accessible materials, because the tosylhydrazones were prepared from cyclohexanones, which were the products of the Robinson annulation of the inexpensive acetondicarboxilyc acid dimethyl ester and the appropriate chalcones.

5. The biphenyl framework was constructed from the iodobenzene derivatives through an Ullmann-coupling. After the suitable transformation of the side chain (***Scheme 7***) the desired phase transfer catalysts were obtained in a ring-closure reaction with different amines (***Scheme 8***).

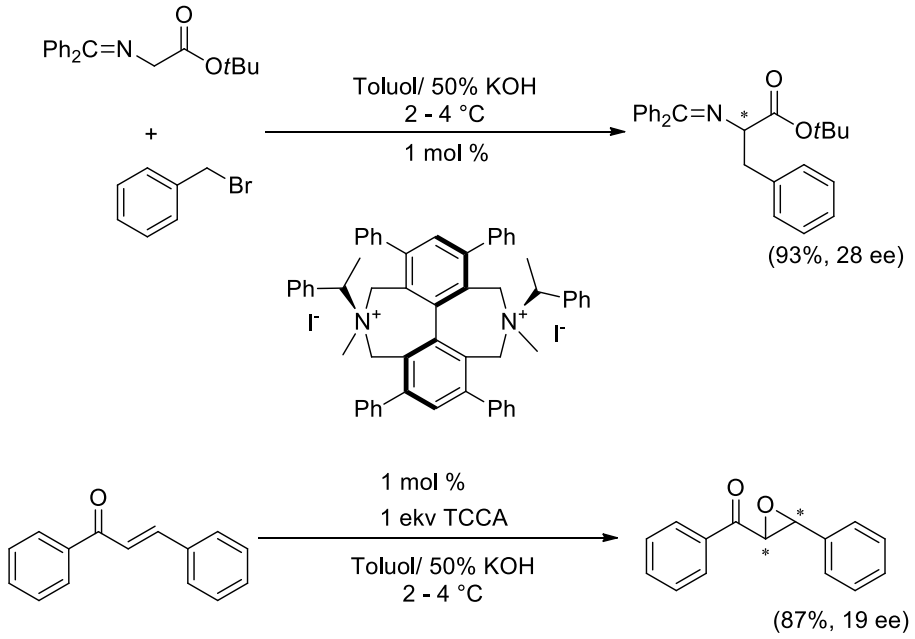


Scheme 7. *Transformation of the side chain*



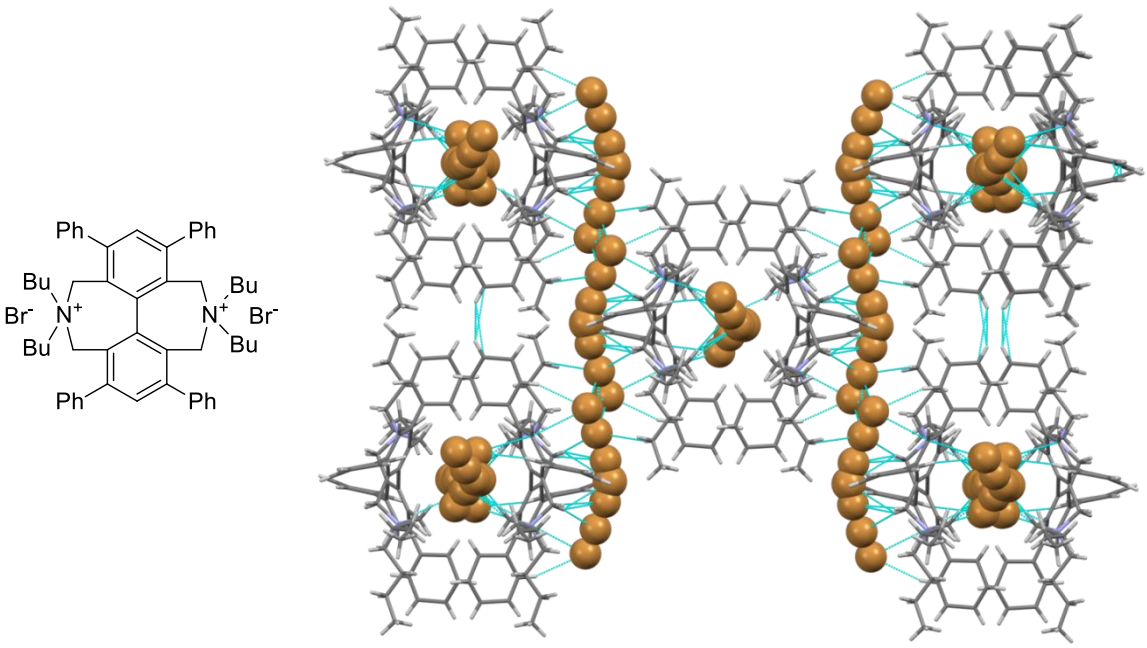
Scheme 8. *Ring-closure reaction of the tetrabromo intermediate*

6. The synthesized PTC catalysts were tested in the alkylation of a protected glycine ester and in the epoxidation of the chalcone. In both cases the expected catalytic activity and only a little enantioselectivity were observed ***(Scheme 9***).



Scheme 9. *Reactions catalysed by the enantiopure catalyst*

7. The catalyst, containing dibutyl groups, crystallized in a highly porous solid structure according to X-ray measurements, which means this compound shows properties that are similar to MOF, COF and HOF structures (***Scheme 10***).



Scheme 10. *The crystal structure of the catalyst containing dibutyl unit*

In the second part of my work, new chiral biphenyl PTC catalysts were prepared in a scalable manner, in which the active center of the successful Maruoka catalyst was doubled.

In the course of the synthesis of the chiral PTC catalyst, 2,3,4,5-tetrasubstituated iodobenzene derivatives were prepared using *de novo* [3 + 3] annulation.

Suitable tosylhydrazones were transformed into the polisubstituated iodobenzenes with a new methodology. The tosylhydrazones were prepared from cyclohexanones, which were the products of the Robinson annulation of the inexpensive acetondicarboxilyc acid dimethyl ester and the appropriate chalcones.

The synthesized PTC catalysts were tested in the alkylation of a protected glycine ester and in the epoxidation of the chalcone. In both cases the expected catalytic activity and only a little enantioselectivity were observed.

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4 Papers Forming the Basis of the Dissertation

„Regioexhaustive functionalization of the carbocyclic core of isoquinoline. Concise synthesis of oxoaporphine core and ellipticine”

Horváth, D. V.; Domonyi, F.; Palkó, R.; Lomoschitz, A.; Soós, T. *Synthesis* **2018**, 50, A-J in Press, DOI: 10.1055/s-0037-1609153

„Polymorphism of a porous hydrogen bond assisted ionic organic framework”

Horváth, D. V.; Holczbauer, T.; Bereczki, L.; Palkó, R.; May, N. V.; Soós, T.; Bombicz, P. *Cryst. Eng. Comm.* **2018** in Press, DOI: 10.1039/c8ce00041g